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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/091,591	03/07/2002	Raymond J. Bergeron	T2315-907789	9684

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1751 PINNACLE DRIVE
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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	**PAPER NUMBER**
1614	

MAIL DATE	DELIVERY MODE
08/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/091,591	BERGERON, RAYMOND J.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

CLAIMS 1-6 ARE PRESENTED FOR EXAMINATION

In view of the Appeal Brief filed on 5/21/2007, PROSECUTION IS HEREBY REOPENED. New Grounds of Rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR § 1.111 (if this Office action is non-final) or a reply under 37 CFR § 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR § 41.31 followed by an appeal brief under 37 CFR § 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR § 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

Ardin Marschel, SPE – AU 1614.

Response to Arguments

Applicant's arguments filed 5/21/2007 (see Appeal Brief) have been fully considered but they are not persuasive with respect to the 35 U.S.C. § 112, 1st Paragraph (Written Description) rejection of claims 1-6. Applicant argues that there is nothing inherently ambiguous or uncertain about a negative limitation or an exclusionary *proviso*. This argument, however, is directed to a

rejection under 35 U.S.C. § 112, 2nd Paragraph, not the present rejection under 35 U.S.C. § 112, 1st Paragraph. Applicant cites *In re Johnson* (223 USPQ 1260) in support of his argument that a claim to a genus with a recital of a negative *proviso* that did not appear in the specification complied with the description requirement. Firstly, it is noted that the citation of *In re Johnson* is incorrect. *In re Johnson* (223 USPQ 1260) as cited by Applicant relates to an obviousness rejection. *In re Johnson and Farnham* (194 USPQ 187) relates to the written description provision of 35 U.S.C. § 112, 1st Paragraph and is applicable here. Regardless, while it is true that a negative *proviso* need not be explicitly recited in specification, *In re Johnson and Farnham* also support the Examiner's position that entities excluded from the claims must be at least positively recited in the specification. In the instant case, claim 1 excludes the *trans* isomer of two distinct compounds. However, only one of these specific compounds is positively recited in the specification (page 8 and page 14). In fact, this compound (CHX(3,4,3-trans)) is the **only** specific compound identified in the specification. Accordingly, Applicant's negative *proviso* excluding CHX(4,4,4-trans) (compound 33 of the '533 patent) has no written basis in the originally filed disclosure. The rejection is maintained for the reasons of record and reiterated below.

Applicant's arguments, see Appeal Brief, filed 5/21/2007, with respect to the rejection(s) of claim(s) 2 under 35 U.S.C. § 112, 2nd Paragraph and claims 1-6 under 35 U.S.C. § 103 as being obvious over U.S. Patent No. 5,962,533 have been fully considered and are persuasive. Therefore, the rejections have been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of U.S. Patent No. 5,889,061 (Issued March 30, 1999).

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are again rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

No support is seen in the specification for the *proviso*, "excluding the *trans* isomers of the compounds having the structures...." as recited in claim 1. The first excluded compound is CHX(3,4,3-*trans*), which is positively recited at pages 8 and 14 of the specification. This is the **only** specific compound identified in the specification. The second excluded compound is CHX(4,4,4-*trans*), which is neither positively nor negatively recited in the specification. Accordingly, Applicant has no written basis for the specific exclusion of CHX(4,4,4-*trans*) from the claims.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2 and 4-5 are rejected under 35 U.S.C. § 102(b) as being anticipated by Frydman *et al.* (U.S. Patent No. 5,889,061; Issued Mar. 30, 1999).[1]

The instant claims recite pharmaceutical compositions comprising an effective amount of a compound having the formula:

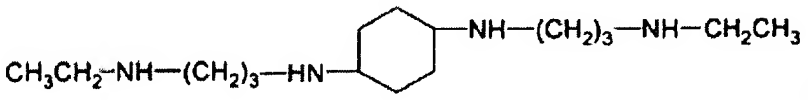
$$R_1\text{-}N^1(R_2)\text{-}(CH_2)x\text{-}N^2H\text{-}Q\text{-}N^3H\text{-}(CH_2)y\text{-}N^4(R_3)\text{-}R_4 \qquad (I)$$

wherein: R_1, R_2, R_3 and R_4 are the same or different and are H, alkyl, cycloalkyl or aralkyl having from 1 to 12 carbon atoms, or a heterocyclic group having from 3 to 10 atoms wherein the hetero atom is said N^1 or N^4;

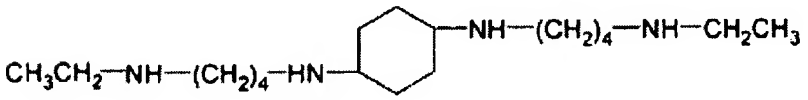
Q is a cycloalkyl group having from 3 to 10 carbon atoms;

x is an integer from 3 to 6, inclusive;

excluding the *trans* isomers of the compounds having the structures:



and



and y is an integer from 3 to 6, inclusive;

and a pharmaceutically acceptable carrier. Dependent claims recite limitations wherein: Q is connected either *cis* or *trans* as the (1,2), (1,3), (1,4), (1,5) or (1,6) isomer (claim 2); x is 3 and y is 3 (claim 4); and x is 3, y is 3, R_1 and R_3 are both H and R_2 and R_4 are both ethyl (claim 5).

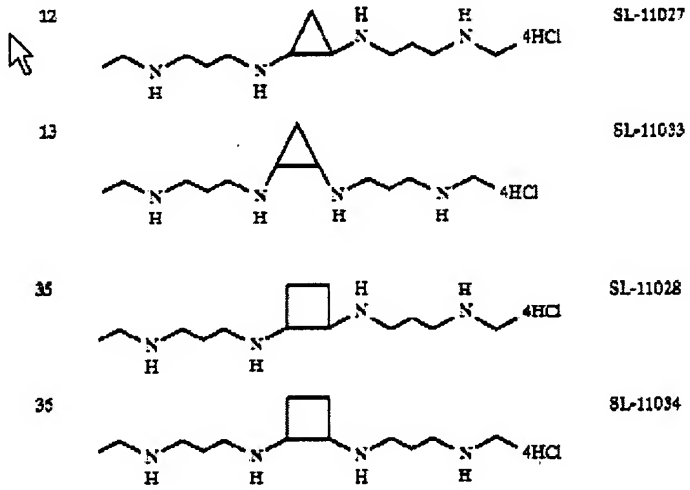
[1] Frydman *et al.* qualifies as prior art under 35 U.S.C. § 102(b) because the earliest effective filing date afforded the instant claims is Dec. 13, 2000 (filing date of 09/734,660 application).

Frydman *et al.* teach compounds of the formula:

E-NH-D-NH-B-A-B-NH-D-NH-E (I)

wherein A is C_2–C_6 alkene, C_3–C_6 cycloalkyl, cycloalkenyl, or cycloaryl; B is independently a single bond, C_1–C_6 alkyl alkenyl; D is independently C_1–C_6 alkyl or alkenyl, or C_3–C_6 cycloalkyl, cycloalkenyl, or cycloaryl; and E is independently H, C_1–C_3 alkyl or alkenyl; and

and pharmaceutically acceptable salts thereof (Abstract; col. 2, lines 1-11). Exemplified compounds of the invention are taught in Table 1. Four of these compounds anticipate the genus recited in instant claim 1.



These compounds anticipate the instantly claimed genus when R_1 and R_4 are ethyl, R_2 and R_3 are hydrogen, x and y are 3, and Q is a cycloalkyl having 3 carbons (SL-11027 and SL-1033) or Q is a cycloalkyl having 4 carbons (SL-11028 and SL-11034). Instant claim 2 recites the limitation wherein Q is connected either *cis* or *trans* as the (1,2) isomer. The above compounds are connected *cis* (SL-11033 and SL-11034) and *trans* (SL-11027 and SL-11028) as the (1,2) isomer, thus anticipating claim 2. As discussed *supra*, the exemplified compounds meet the limitations of instant claims 4 and 5 (x is 3 and y is 3; x is 3, y is 3, R_1 and R_3 are both H and R_2 and R_4 are both ethyl). Pharmaceutical compositions comprising the compounds of the invention

in a pharmaceutically acceptable carrier and in an effective amount are taught at column 21, line 3 to column 22, line 9. For example, Frydman *et al.* teach formulating the compounds of the invention in pharmaceutically acceptable carriers (col. 21, lines 35-44 and lines 52-55).

It is well established that intended use does not impart patentability in a composition claim. See *In re Zierden*, 411 F.2d 1325, 1329, 162 USPQ 102, 104 (CCPA 1969):

> A mere statement of a new use for an otherwise old or obvious composition cannot render a claim to the composition patentable. As we said in *In re Lemin*, 51 CCPA 942,326 F.2d 437,140 USPQ 273,276 (1964),
>
> > Appellants are clearly correct in demanding that the subject matter as a whole must be considered under 35 U.S.C. 103. But in applying the statutory test, the differences over the prior art must be more substantial than a statement of the intended use of an old composition. ... It seems to us that the composition ... would be exactly the same whether the user were told to cure pneumonia in animals with it ... or to promote plant growth with it (as here). The directions on the label will not change the composition....

See also, *In re Spada*, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990) ("[t]the discovery of a new property or use of a previously known composition, even when that property and use are unobvious from the prior art, cannot impart patentability to claims to the known composition"). Accordingly, the claims simply require a composition comprising a compound of formula I and a pharmaceutically acceptable carrier. As such, the compositions of Frydman *et al.* clearly anticipate the instantly claimed compositions.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3 and 6 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Frydman *et al.* (U.S. Patent No. 5,889,061; Issued Mar. 30, 1999) as applied to claims 1-2 and 4-5, *supra.*

Instant claim 3 recites the limitation wherein Q is cyclohexyl in the compounds of Formula I. Claim 6 recites the limitation wherein Q is cyclohexyl; x and y are 3; R_1 and R_3 are both H, and R_2 and R_4 are both ethyl.

Frydman *et al.* do not explicitly exemplify compounds wherein the C_3-C_6 cycloalkyl is cyclohexyl. Exemplified compounds of the invention are drawn to cyclopropyl and cyclobutyl moieties (Table 1). However, Frydman *et al.* teach that "A" (Q in the instant claims) can be C_2-C_6 alkene, C_3-C_6 cycloalkyl, cycloalkenyl, or cycloaryl (Abstract). Thus, with respect to cycloalkyl groups, there are only four possible substitutions: cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. The inventors made and exemplified cyclopropyl and cyclobutyl substituted compounds (Table 1) having identical substituents as those recited in instant claim 6 (*i.e.*, x and y are 3; R_1 and R_3 are both H, and R_2 and R_4 are both ethyl).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Scope and Content of the Prior Art:

In the instant case, Frydman *et al.* teach a genus of compounds having a limited number of alternate substitutions. With respect to the instantly claimed sub genus of compounds having a cyclohexyl group, Frydman *et al.* teach that the compounds of the invention can be substituted with a C_3-C_6 cyclohexyl (four possible substitutions). The compounds of Frydman *et al.* are taught to be useful in the treatment of cancer. In this regard, compounds having a cyclopropyl (C_3) and cyclobutyl (C_4) substitution were exemplified and tested for anticancer activity (Table 1 and Table 2). The number of species encompassed by the genus taught in Frydman *et al.* is relatively small. For example, there are only twelve possible substitutions for A, eight for B, eighteen for D, and thirteen for E. The majority of these substitutions are structurally related and represent homologous series (*e.g.*, C_2-C_6 alkene, C_3-C_6 cycloalkyl, C_1-C_6 alkyl, etc.).

Differences Between Prior Art and Claims:

The closest disclosed prior art species to the sub genus instantly claimed are the compounds designated SL-11027, SL-11033, SL-11028, and SL-11034 in Frydman *et al.* (Table 1). These species differ from the instantly claimed genus **only** in the number of carbons present in the cycloalkyl substitution (*i.e.*, C_3 and C_4 versus C_6); all other substituents are identical.

Level of Ordinary Skill in the Art:

A person having ordinary skill in the art at the time of the present invention would generally be a medical chemist well practiced in the art of structure-activity relationships as they pertain to chemical modifications and biological activity.

Objective Evidence and Motivation:

In light of the above findings relating to the three *Graham* factors, the skilled artisan would have been motivated to make the claimed sub genus of compounds and to formulate them in a pharmaceutical composition. See, *e.g.*, *Deuel*, 51 F.3d at 1557, 34 USPQ2d at 1214 ("[A] *prima facie* case of unpatentability requires that the teachings of the prior art suggest *the claimed compounds* to a person of ordinary skill in the art." (emphasis in original)); *In re Lalu*, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed. Cir. 1984) ("The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound."). Considering the size of the prior art genus, especially with respect to the limited number of cycloalkyl groups contemplated by Frydman *et al.*, one skilled in the art could readily envisage each member of the sub genus of compounds containing C_3-C_6 cycloalkyl groups. *In re Petering*, 301 F.2d 676, 681, 133 USPQ 275, 280 (CCPA 1962). Frydman *et al.* also expressly suggest and motivate the selection of a cyclohexyl substitution. For example, cyclopropyl and cyclobutyl groups introduce constraints into otherwise flexible spermine molecules (col. 4, lines 53-67) and a "cyclohexyl moiety" can be introduced *in a similar manner* to the cyclopropyl and cyclobutyl constraints (col. 5, lines 6-7). The skilled artisan would recognize that the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl series of homologs could be used to evaluate conformational constraints in spermine analogs (*i.e.*, cyclopropyl provides the most constraint whereas cyclohexyl provides the least constraint). As such, making cyclopentyl and cyclohexyl substituted spermine analogs having the same substituents as the explicitly disclosed cyclopropyl and cyclobutyl analogs would be the next logical step.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art to also make the cyclopentyl- and cyclohexyl-substituted compounds and to formulate them into pharmaceutical compositions. This is especially true given the limited number of cycloalkyl substituents contemplated in Frydman *et al.* (*i.e.*, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl). Two of these four cycloalkyls were exemplified in the reference. Accordingly, the skilled artisan would have been highly motivated to choose the instantly claimed cyclohexyl substitution, based on the reasonable expectation that structurally similar species usually have the same properties. See, *e.g.*, *Dillon*, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also *Deuel*, 51 F.3d at 1558, 34 USPQ2d at 1214 ("Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties.").

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Patent Examiner
AU 1614

August 22, 2007

Ardin H. Marschel 8/24/07
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SUPERVISORY PATENT EXAMINER